No. 12-398

IN THE

Supreme Court of the United States

ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF *AMICI CURIAE* OF THE NATIONAL WOMEN'S HEALTH NETWORK, REPRODUCTIVE HEALTH TECHNOLOGIES PROJECT, DISABILITY RIGHTS LEGAL CENTER, FORWARD TOGETHER, THE CENTER FOR GENETICS AND SOCIETY, THE PRO-CHOICE ALLIANCE FOR RESPONSIBLE RESEARCH, ALLIANCE FOR HUMANE BIOTECHNOLOGY, G. MICHAEL ROYBAL, MD, MPH, AND ANNE L. PETERS, MD IN SUPPORT OF PETITIONERS

DEBRA GREENFIELD
Counsel of Record
INSTITUTE FOR SOCIETY AND GENETICS
UNIVERSITY OF CALIFORNIA,
LOS ANGELES
1323 Rolfe Hall, Box 957221
Los Angeles, CA 90095
(310) 267-4990
dgreenf@ucla.edu

Attorney for Amici Curiae

244115

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INTEREST OF *AMICI CURIAE*

Amici Curiae are health and social justice advocates, experts in policy issues concerning women's health, and health disparities for socio-economically disadvantaged women and women of ethnic and racial backgrounds. *Amici Curiae* educate community-based organizations about the implications of genetic technologies for women's health, and advocate for just public policy. *Amici Curiae* also include physicians/researchers working in our burdened healthcare system, experts in the clinical care and treatment of underserved populations they understand the importance of genetic technologies for preventative medicine, treatments, and potential cures.

Amici Curiae are deeply concerned about the Federal Circuit's decision to allow the patenting of the BRCA 1/2 genes. *Amici* understand that Myriad's patents monopolize molecules and genes that embody essential scientific principles, and recognize that the preemption of this knowledge inhibits innovative work in research and treatments for breast and ovarian cancer, with resultant harms for the communities and patients they serve.[1]

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1. The parties have consented to the filing of this brief and letters of consent to the filing were lodged with the Clerk of the Court. Counsel of record for all parties received timely notice of *amici curiae's* intention to file this brief, per Supreme Court Rule 37. No counsel for a party authored this brief in whole or part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amici curiae* and their members or their counsel made a monetary contribution to its preparation or submission.

Amicus Curiae **The National Women's Health Network** aspires to a health care system that is guided by social justice and reflects the needs of diverse women by developing and promoting a critical analysis of health issues which affect policy and support consumer decision-making, providing evidence-based information free from corporate influence. They have particular expertise in women's health issues as a result of their research and evaluation of emerging drugs, devices, and treatments and their impact on women's health.

Amicus Curiae **Reproductive Health Technologies Project** is a national non-profit organization working on behalf of every woman to achieve access to the safest and most effective methods for protecting their health, by ensuring that new technologies are developed and introduced with appropriate safeguards, a well-informed consumer constituency, and broad based public support. Bringing together experts, using solid science and clinical data to influence political outcomes, and seeking consensus among diverse communities, RHTP is a powerful vehicle for public education and policy development around health technologies.

Amicus Curiae **Disability Rights Legal Center** champions the rights of people with disabilities through education, advocacy, and litigation. Together with the Loyola University School of Law at Los Angeles, they direct the **Cancer Legal Resource Center**. Since 1997, the CLRC has provided free information and resources on cancer-related legal issues to cancer survivors, caregivers, health care professionals, employers, and others coping with cancer, serving over 310,000 people through conferences, seminars, workshops, education and outreach

programs, and other cancer community activities. To this end, the CLRC runs a free and confidential national Telephone Assistance Line that assists individuals with cancer and genetic-related legal issues, including the costs of testing, insurance coverage, employment, and access to health care and government benefits.

Amicus Curiae **Forward Together** is a nonprofit community-based multi-racial organization that engages in grass-roots action and training community leaders, working in communities of color to ensure that women and adolescents have the information they need to improve their own health status, and believing in policy that enables *all* people to have the economic, social, and political power and resources necessary for decision-making regarding their bodies.

Amicus Curiae **The Center for Genetics and Society** is a nonprofit public affairs organization working to encourage responsible uses and effective societal governance of genetic, reproductive and biomedical technologies. Providing accurate information regarding these technologies to the public, CGS works with civil society leaders, health professionals, scientists, and others who share a commitment to advancing the public interest in the development of policy regarding human biotechnologies.

Amicus Curiae **The Pro-Choice Alliance for Responsible Research** is a coalition of reproductive rights and justice advocates, bioethicists, academics, and community leaders promoting accountability, safety and social justice in bio-medical research from a women's rights perspective. Since 2004, PCARR has been

providing research and legal analysis to policymakers and consumers, and engaging with administrative agencies to ensure that women's health outcomes are protected in the implementation of new biotechnologies.

Amicus Curiae **Alliance for Humane Biotechnology** is a non-profit association that conducts outreach and education on the social implications of human genetics and works for a culture of science that places the health and welfare of people above financial interests.

Amicus Curiae **G. Michael Roybal, MD, MPH** is the Medical Director of the Roybal Comprehensive Health Center (CHC), established to address the inequity of communities and individuals without access to affordable healthcare. Dr. Roybal has spent his career working with the Department of Health Services for Los Angeles County, focusing on healthcare redesign and reform in an attempt to improve healthcare delivery for underserved populations.

Amicus Curiae and **Anne L. Peters, MD**, is the Director of the Diabetes Clinic at the Roybal Comprehensive Health Center (CHC) and a Professor at the USC Keck School of Medicine. An internationally known expert in the field of treatment for diabetes, she has received numerous grants to improve health environments and reduce obesity rates in underserved populations. Her work at the CHC provides over 80,000 yearly patient visits, mostly for the uninsured. A similar program she developed is situated at five additional safety-net sites in Los Angeles County.

SUMMARY OF ARGUMENT

This Court recently considered the nature of exceptions to the categories of patentable subject matter according to 35 U.S.C. §101, *Mayo v. Prometheus*, 132 S. Ct. 1289 (2012), and ordered that this case be remanded in light of *Mayo* and its foundational principles. *Association for Molecular Pathology, et al., Petitioners, v. Myriad Genetics, Inc., et al*, ___ U.S. ___, 132 S. Ct 1794, 182 L. Ed.2d 613 (2012). Deciding the patent eligibility of a claim to a diagnostic process, *Mayo* clarified the law/product of nature doctrine by explaining what necessitates turning a patent-ineligible law of nature into a patentable application of that law. *Mayo* at 1289. *Amici* argue that the Federal Circuit failed to apply the essential principles delineated in *Mayo* to the issue of whether isolated DNA/cDNA molecules are exceptions to the statutory categories, and that the allowance of Myriad's patents on the BRCA 1/2 genes results in grave harms for the health of women and their families particularly those who are socio-economically disadvantaged or of ethnic or minority backgrounds.

This Court in *Mayo* described the nature of the medical diagnostic method at issue as a relationship, a law of nature, *id*., 132 S. Ct. at 1297, as nothing of significance had been added to the underlying natural phenomenon to make it a patentable application of that law. *Id* at 1297-1300. Significantly, *Mayo* considered the patents' preemptive effect relevant to their conclusion that the resultant inhibition of innovation rendered the process ineligible for patent protection. *Id.*at 1302.

Amici argue that *Mayo's* analysis is equally applicable to a composition claim. Myriad's patents on the BRCA

1/2 genes are for phenomena of nature analogous to the claimed relationship in *Mayo*. Lacking an inventive concept, nothing of significance has been added to the law/product of nature itself to render it patent-eligible. Myriad's claims to the isolated DNA/cDNA molecules of those genes simply describe natural phenomena which are not markedly different whether inside or outside the human body.

The Federal Circuit stated that the case was *not* about whether those at increased risk of breast cancer were entitled to second opinions, whether one company should hold a patent or license covering a test which may save people's lives, or whether other companies should be excluded from a market encompassed by such a patent. *Association for Molecular Pathology v. United States PTO*, 2012 U. S. App. LEXIS 17679, 50 (August 16, 2012). *Amici* disagree, and argue that these examples illustrate *Mayo's* essential concern: patents which preempt too much future use of laws of nature inhibit and impede innovation.

Myriad's patents on isolated DNA/cDNA molecules preempt the use of laws of nature regarding the human genome. Giving a cancer patient a second opinion based upon the vital genetic informational content of the BRCA 1/2 genes is *an infringement on Myriad's patents*. Only one company, Myriad, can use these scientific principles which contain keys to saving lives, *otherwise an infringement on Myriad's patents has occurred.* Excluded from the market, and the marketplace of ideas, scientists, researchers, workers in biomedical communities, clinicians, and patients attempting to study and use these scientific tools *infringe Myriad's patent claims.* These patents foreclose innovation in biomedical research and healthcare causing grave harms for the

health of women and their families, particularly those who are socio-economically disadvantaged or ethnic and racial minorities.

The important principles delineated in the *Mayo* decision are applicable to the case at bar. Myriad's claims are for patent-ineligible laws and products of nature and should be invalidated.

ARGUMENT

I. *Mayo* Controls the Issue of the Patentability of Myriad's Claims.

The Federal Circuit erred by failing to apply the enunciated principles of *Mayo* to the issue in the present case, whether Myriad's patent claims to isolated DNA/cDNA molecules are patent-ineligible exceptions to the statutory categories, or patent-eligible compositions of matter according to 35 U.S. §101. *Ass'n*, 2012 U.S. App LEXIS 17679 at 51.

"Laws of Nature, natural phenomenon, and abstract ideas are not patentable subject matter under §101 of the Patent Act." *Mayo,* 132 S. Ct. at 1293, citing *Diamond v. Diehr*, 450 U. S. 175, 185, 101 S. Ct. 1048, 67 L. Ed. 2d 155 (1980). Additionally, "phenomenon of nature, though just discovered… are not patentable, as they are the basic tools of scientific and technical work." *Id.*, citing *Gottschalk v. Benson,* 409 U. S. 63, 67, 93 S. Ct. 253, 34 L. Ed. 2d 273 (1972). *Mayo* acknowledged that "monopolization of those tools through the grant of a patent might tend to impede innovation more than it would tend to promote it." *Mayo*, *supra.*

Mayo considered whether a process for measuring the relationship between concentrations of metabolites in the blood and a likelihood that a certain dosage of drug would prove effective or cause harm, was patent-eligible subject matter. *Id.*,132 S. Ct. at 1296. Despite administering a drug to trigger the manifestation of the relationship, the relationship existed apart from any human action and was an entirely natural process. *Id.* at 1296-97. The claims did not rest upon inventive concepts as nothing in the steps of the process added anything of significance to the law of nature itself. *Id.* at 1298. The process was essentially for the underlying relationship, a patent-ineligible law of nature. *Id.* at 1302.

Mayo recognized that patenting basic scientific tools posed a danger for future innovation, particularly if more future innovation was foreclosed than justified by the underlying discovery. *Id.* at 1301. Although the claimed law of nature in *Mayo* was narrow, these concerns were implicated, affecting the ability of doctors to determine treatment options and threatening the development of more refined treatment recommendations which would combine features of the correlation with later discoveries involving aspects of human physiology and biology. *Id.* at 1302. This preemption of future uses of laws of nature reinforced this Court's conclusion that the processes were not patent eligible. *Id.*

The Federal Circuit erred in its application of *Mayo* by resting on two premises: 1) the isolated DNA/cDNA molecules were compositions of matter not processes, therefore *Mayo* did not control the issue of patent eligibility; and 2) the isolated molecules were not products of nature. *Ass'n,* 2012 U. S. App. LEXIS 17679 at 51-55. In

light of *Mayo*, patent claims on isolated DNA/cDNA are directed to patent-ineligible laws and products of nature.

Myriad's claimed molecules of the BRCA 1/2 genes are the embodiment of important information and pre-existing scientific principles; both their structure and function encodes the relationship between a DNA molecule and a protein. The patent claims disclose the sequential information embodied in the molecules, they merely describe this relationship and do not add any inventive concepts to this underlying law and product of nature. Isolating and synthesizing these molecules do not change their identity, despite minute structural changes they are not markedly different from what is found in nature.

These molecules are analogous to the law of nature delineated in *Mayo* as well as products of nature. Myriad's patents preempt basic scientific knowledge and tools, tie up too much of their future use, and impede rather than promote innovation. In accordance with *Mayo*, this Court should grant certiorari to correct the Federal Circuit's flawed decision and hold these claims ineligible for patent protection.

A. Isolated DNA/cDNA Molecules of the BRCA 1/2 Genes are Laws of Nature:

The process in *Mayo* claimed a correlation, primarily a relationship between concentrations of metabolites in the blood and the likelihood that a certain dosage of drug would prove effective or cause harm: "The relation is a consequence of the ways in which thiopurine compounds are metabolized by the body-entirely natural processes." *Mayo*, 132 S.Ct. at 1297. Despite the human action of

administering a drug to manifest the relation, "a patent that simply describes that relation sets forth a natural law." *Id.* at 1298.

The embodied informational content of the claimed isolated DNA/cDNA molecules is similarly, a relationship, a law of nature. DNA is a chemical molecule composed of four standard repeating chemical units, adenine, thymine, cytosine and quinine (aka, A, T, C, G) known as nucleotides, or bases. *Ass'n for Molecular Pathology v. United States PTO*, 702 F. Supp. 2d 181, 193 (S. D. N. Y. 2010). The ordering of these bases is described as nucleotide sequences, DNA sequences or gene sequences. *Id.* at 194. Gene sequences constitute biological information, describing the structural and chemical properties of a particular DNA molecule that is the cellular "blueprint" for the productions of proteins, and are of a double nature: they are both "chemical substances of molecules as well as physical carriers of information, i.e., where the actual biological function of this information is coding for proteins." *Id.* at 194, 228, citing Strauss Decl. at P 20.

For patenting purposes, it is the structures themselves which are useful. *See,* Dan Burk, *The Problem of Process in Biotechnology*, 43 Hous. L. Rev. 561, 582-87 (2006). The interest is not in the string of 'letters' of the sequence, but "in…building informational structures-the molecules that are the conduit for information transfer." *Id.* at 586-87. These informational structures are the sole content of Myriad's isolated DNA/cDNA claims, the embodiment of the specified nucleotide sequences relating to the BRCA 1/ 2 genes. *See,* e.g. claims 2, 5, 6, 7 of U. S. Patent No. 5,747,282; claims 1, 6, 7 of U. S. Patent No. 5,837,492. *Id.* at 212; Claim 1 of the '282 patent is for "1) An isolated

DNA coding for a BRCA-1 polypeptide[protein], said polypeptide having the amino acid sequence set forth in SEQ ID NO: 2." U.S. Patent No. 5,747,282 col. 154 11.56-58 (filed June 7, 1995).

This ordering of the chemical bases, the arrangement of nucleotides is a relationship, an entirely natural process. The structure of the nucleotides in the molecule enables the instructions for the building of proteins in the human body, or within identical and synthesized DNA. The ordering is a pre-determined relationship, a correlation that reveals a genetic susceptibility to breast and ovarian cancers in the BRCA 1/2 genes, a pre-existing scientific principle. The relationship remains unchanged apart from the human action of isolation or synthesis. The claims "simply describe the relations" between the order of the nucleotides and their resulting chemical, structural, and functional content. The claims merely "point out a set of facts that exist in the world…" *Mayo v. Prometheus*, 2011 U. S. Trans. LEXIS 76 *39, *43 (2011). As such they are patent-ineligible laws of nature.

B. Claims to Isolated DNA/cDNA Molecules do not Contain Inventive Concepts and are Patent-Ineligible Products of Nature.

Processes using a natural law must also contain an inventive concept so that the patent is "significantly more than a patent upon the natural law itself." *Mayo*, 132 S. Ct. at 1294. The steps in *Mayo's* claimed process--administering, determining, and a wherein step-- simply told doctors to gather data and draw inferences in light of the correlations. *Id.* at 1298. The steps were well understood, routine, conventional activity already

engaged in by the scientific community. *Id.* The claims were not transformative, and did not make a claimed law of nature a patentable application of that law. *Id.*

Claims to isolated DNA/cDNA molecules do not rest on inventive concepts. The claim terms indicating isolation or synthesis do not add anything of significance to render these laws and products of nature patent-eligible. "Isolated" simply denotes "a nucleic acid…which is substantially separated from other cellular components which naturally accompany a native human sequence." *Ass'n*, 702 F. Supp at 213, n.30. Having been derived from mRNA, a synthesized cDNA molecule represents an exact copy of one of the protein coding sequences encoded by the original genomic DNA. *Id*. citing Leonard Decl. P 75.

Well-established laboratory techniques are used in isolating, extracting the claimed molecules from their cellular environment. *Id.* at 198. DNA sequencing processes used to determine the ordering of the nucleotides within a DNA molecule are well known techniques understood and routinely performed by scientists skilled in molecular biology. *Id.* at 200. These conventional activities add nothing to the phenomena of nature itself.

Disregarding *Mayo,* the Federal Circuit relied on the test established in *Diamond v. Chakrabarty*, 447 U. S. 303, 100 S. Ct. 2204, 65 L. Ed. 2d 144 (1980) to determine that the claimed molecules were "markedly different" from what existed in nature, and thus patent-eligible. *Ass'n,* 2012 U. S. App, LEXIS 17679 at 56-61. The court reasoned that while DNA molecules exist in the body (native DNA) as part of a "large structural complex," (i.e., part of a chromosome), isolated DNA is "a free standing

portion of a larger natural DNA molecule," which had been cleaved (i.e., had covalent bonds in its backbone chemically severed, or synthesized to consist of just a fraction of a naturally occurring DNA molecule). *Id.* at 61-62. Resulting from this cleavage or synthesis, the isolated DNA/cDNA was declared a distinctive chemical identity, and thus "markedly different" from patent-ineligible products of nature. *Id.*

The minute change in physical structure does not make the isolated or synthesized molecules, "*markedly* different" from their native state or impart a distinctive identity. Rather, the Federal Circuit dismissed established biological truths regarding the functionality of the molecules. *Id.* Unlike other chemicals, the molecules describe the nucleotide sequences which direct the proteins, cells and organs which make up the body. This biological function is the defining and identical characteristic of DNA/cDNA both before and after isolation or synthesis, and thus, these molecules are not markedly different from their native state. In fact, if these isolated or synthesized molecules had a truly distinctive chemical identity or were markedly different from what exists in nature their applications in research and diagnostics could not use the natural biological characteristics of DNA sequences to code for a protein and to anneal to its complementary nucleotide sequence. Products of nature, they "…serve the ends nature originally provided." *Funk Bros. Seed Co v. Kalo Inoculant Co.,* 333 U. S. 127, 131, 68 S. Ct. 440, L. Ed. 588 (1948).

Myriad's claims do not rest upon inventive concepts, as the techniques of isolation and synthesis are not transformative.

C. Myriad's Patents Preempt Phenomena of Nature, Inhibiting Innovation and Limiting Future Discoveries in Biomedical Research and Development.

A patent is a right which allows the exclusion of others from making, or using the patented invention. 35 U.S.C. § 271(a) (2000). This Court has repeatedly emphasized the concern that "patent law not inhibit further discovery by improperly tying up the future use of laws of nature," as this might impede, rather than promote innovation. *Mayo*, 132 S. Ct. at 1301.

This Court's precedents, "…warn us against upholding patents that too broadly preempt the use of a natural law." *Id*, citing *O'Reilly v. Morse*, 56 U.S. 62, 14 L. Ed. 601 (1854). Examples include general claims for underlying scientific principles, *id*, abstract and sweeping claims to a mathematical formula which covered both known and unknown uses of that formula, *id,* citing *Benson*, 409 U.S. at 67, 93 S. Ct. 253, 34 L. Ed. 2d 273, concepts involving business transactions which precluded the use of its approach in all fields, *id,* citing *Bilski v. Kappos*, 130 S. Ct. 3218, 177 L. Ed. 2d 792 (2010), and a formula that could be preempted from use in a broad range of possible uses. *Id*, citing *Parker v. Flook,* 437 U. S. 584, 586, 98 S. Ct. 2522, 57 L. Ed. 2d 451 (1978).

Although the process claimed in *Mayo* was a narrow law it implicated these concerns. *Mayo*, 132 S. Ct. at 1302. "It told a doctor to measure metabolite levels and to consider them in light of the statistical relationships they describe," *id,* so that relationship cannot be used by doctors in subsequent treatment decisions to determine

whether or not the treatment should change. *Id.* The correlation cannot be used to develop more refined treatment options when combined with "later discovered features of metabolites, human physiology or individual patient characteristics." *Id.* The recognition that the "patents tie up too much future use of laws of nature" reinforced the Court's conclusion that the process was not patent-eligible. *Id.*

Myriad's patents on isolated DNA/cDNA "too broadly preempt natural laws." They are "general," preempting *all uses* of fundamental principles of molecular biology and genetics. The claims are "sweeping" covering both "known and unknown uses" of the embodied information of the BRCA 1/2 genes, preempting this knowledge from all fields of biomedical research and healthcare, including a broad range of potential uses for diagnosing and treating breast and ovarian cancer.

Specific claims are illustrative. Claim 5 of the '282 patent covers any isolated DNAs "having at least 15 nucleotides" of the BRCA 1 gene, thus the claim covers the entire BRCA 1/2 genes. The patents cover both known and unknown mutations for increased susceptibility to breast and ovarian cancer, e.g., Claim 6 of the '492 patent is "directed to any DNA nucleotide encoding any mutant BRCA 2 protein that is associated with breast cancer," including all possible mutations and variations found within those genes. These patents give Myriad the right to exclude anyone from using the DNA of the BRCA 1/2 genes, or copies of these genes outside the human body. The patents restrict all research and clinical testing of the BRCA 1/2 genes. Unlike patents on new drugs, no one can "invent around" Myriad's patents as one cannot

invent a molecule of DNA which encodes the protein which embodies the genetic information of an individual's BRCA 1/2 genes.

The practical implications of this broad preemption inhibit rather than promote progress and innovation. Because Myriad's patents give them a monopoly on genetic testing for breast and ovarian cancer in the United States, like the physicians in *Mayo* unable to change their treatment options, physicians in our country cannot give second opinions regarding a diagnosis for the disease. Like the physicians in *Mayo* unable to refine their treatment methods, physicians treating breast and ovarian cancer are unable to refine their treatment methods because basic biomedical research and research and the development of alternative genetic testing methods have been restricted by Myriad's monopolies on the BRCA 1/ 2 genes. These patents have limited scientific discoveries and will continue to inhibit innovation.

Clinical researchers and laboratory directors have expressed real fears that they will be prevented from doing their work by patent holders. *See,* Richard Gold and Julia Carbonne, *Myriad Genetics: In the Eye of the Policy Storm*, 12 Genetics in Medicine S39 (2010) [hereinafter "Gold"]. These patents negatively affect follow-on public research about the BRCA genes as researchers forego about one in ten research publications as a result. *See Secretary's Advisory Committee on Genetics, Health & Society: Gene Patents and Licensing Practices and their Impact on Patient Access to Genetic Tests,* 4-2010, at A-27[hereinafter "*Report*"].

Ambiguity regarding the possibility of infringement liability inhibits innovation, as scientists avoid work, or "are wary of public reporting results." *Id.* Myriad has not clarified the concept of "infringing activities," or publicly confirmed in writing, their assertion that their patents are not enforced against researchers. *Id.* at A26-27.

Scientists expressed concerns about contributing their research on the BRCA genes to public databases. Gold, *supra* at S44. A university researcher was specifically told *not* to contribute his findings of new mutations. *Id.* In 2004, Myriad stopped contributing data concerning "variations of unknown significance" (VUS) accumulated as a result of their exclusive testing, to the NIH open access Breast Cancer Information Core mutation database, and ceased publishing information regarding these important discoveries in peer-reviewed literature, significantly impeding research. John Conley, Dan Vorhaus, Robert Cook-Deegan: Genomics Law Report, March 1, 2011: *How Will Myriad Respond to the Next Generation of BRCA Testing*, *available at* http://www.genomicslawreport.com/index.php/2011/03/01/how-will-myriad-respond-to-t.

Myriad is the sole provider of genetic testing in the U.S., and has stopped other laboratories from genetic testing. *Report* at 40. Due to the breadth of Myriad's patents, the development of alternative or improved testing methods is diminished. 53% of clinical laboratories do not develop new or improved genetic tests, Mildred K. Cho, et al., *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Service,* 5 J. Molecular Diagnostics, 3, 5 (2003), and researchers have stated that Myriad prevented the development of improved BRCA 1/2 tests. See Gold, *supra* at S44. Any research resulting

in a commercial or clinical service infringes Myriad's patents, notably "…the assessment of technology by third parties, e.g. to evaluate a test for sensitivity, specificity, or positive predictive value." See, Ozdemir, et al, *Shifting Emphasis from Pharmacogenomics to Theragnostics*, Nature Biotechnology, Vol. 24 No. 8 (2006).

Myriad's patents inhibit future innovation in the area of personalized medicine, whose development rests upon genotype-phenotype associations (e.g. BRCA 1/2 mutations and the susceptibility to breast and ovarian cancer). *See*, Roger D. Klein, MD, JD, *Gene Patents and Personalized Medicine,* 2012, American Society of Clinical Oncology. New methods of testing for these associations, able to detect millions of genetic variations and mutations in thousands of genes or even the entire genome will guide treatments, drug dosages and prevention for numerous diseases. However, "If we are to enter the next stage of personalized medicine, we cannot do so by parceling out information-genomes do not work that way, pleiotropy… doesn't stop at the lines drawn by the USPTO." Zachary Russ, *The Holes in Whole Genome Sequencing,* Genetic Engineering & Biotechnology News, *available at*: http://www.genengnews.com/blog-biotech/the-holes-in-whole-genome-sequencing/676 .

"Patent thickets, blocking patents, and high transactions costs" threaten the use of these next generation innovations in genetic testing, such as whole genome sequencing (WGS). *Report* at 50-51. Fearing liability, laboratories using multiplex tests are not reporting results to patients or sending clinicians the results of tests involving patent protected genes. *Id*. Broad patents such as Myriad's isolated DNA/cDNA

claims create uncertainty leading to high transaction costs. WGS industries may need to examine specific patent claims for "all or many of the thousands of human genome sequences subject to patent protection." Dan Vorhaus and John Conley, Genomics Law Report, *Whole Genome Sequencing and Gene Patents Coexist (For Now)*, August 11, 2009, available at: http://www.genomicslawreport.com/index.php/2009/08/11/whole-genome-sequencing-and. The patents potentially affect the use of WGS in assessing for risk or existence of disease, and thus, patient care. National Society of Genetic Counselors, Position Statement of Human Gene Patents, available at: http://www.nsgc.org/Advocacy/PositionStatements/tabid/107/Default.aspx (2010).

Exome sequencing, targeted sequencing restricted to the protein-coding subset of human genes, is based upon an "enrichment of targeted DNA regions by hybridization with probes." Patricia F. Dimond, PhD, *Exome Sequencing Finds Sweet Spot Between Whole-Genome and Targeted Sequencing,* Genetic Engineering & Biotechnology News, *available at*: http://www.genengnews.com/keywordsandtools/print/3/25217/ . The technique's costs relating to data collection, storage and analysis are significantly less than those in WGS techniques, and also lead to the discovery of highly pertinent variants. *Id.* However, "exome sequencing is more likely to face IP issues….because gene patents typically cover methods that would specifically target or enrich for the gene." Monica Heger, *Interpretation Remains Key Challenges in Clinical Sequencing; Patents May Impede Return of Results.* Genome Web, June 27, 2012. Available at: http://www.genomeweb.com/print/1096581.

The potential for infringement using these new methods could "slow some promising clinical technologies." Subhashini Chandrasekharan and Robert Cook Deegan, *Gene Patents and Personalized Medicine, what Lies Ahead?* Genome Medicine, 2009, 1:92. For example, holdout problems might result when drug manufacturers creating targeted therapies "do not own the underlying molecular pathological relationships." Klein, *supra* at 82.

Myriad's patents illustrate these concerns. Numerous cancer patients with BRCA 1/2 mutations have a negative family history, and do not qualify for testing according to Myriad's criteria. Walsh, Lee, Casadei, Thorton, Stray, Pennil, Nord, Mandell, Swisher, and Mary-Claire King; PNAS Early Edition, *Detection of Inherited Mutations for Breast and Ovarian Cancer Using Genomic Capture and Massive Parallel Sequencing,* www.pnas.org/cg/10.1073/pnas [hereinafter "King"]. However, the development of specific treatments, inhibitors which effectively kill BRCA 1/2 mutated carcinomas having *therapeutic* as well as preventive applications, necessitates an increased need for identifying BRCA 1/2 mutations in women with breast and ovarian cancer through testing, which is restricted by Myriad's exclusive test on the patented sequences. *Id.*

The monopolization of the BRCA 1/2 genes tie up too much of their future use. The resultant inhibition of innovation in biomedical research and healthcare treatment is not justified by Myriad's original discovery.

II. Myriad's Patents Diminish the Availability and Quality of Healthcare for Women and their Families, Particularly Those Who are Socio-Economically Disadvantaged, and/or Ethnic or Racial Minorities.

Myriad's patents have implications for the health of women and their families. While the average woman in this country has around a 12%-13% risk of developing breast cancer in her lifetime, women with BRCA mutations face a cumulative risk of between 50% - 80% for breast cancer and a 20%-50% cumulative risk of ovarian cancer. *Ass'n.,* 2012 U. S. App. LEXIS at 18. Testing for BRCA mutations is critical for decisions regarding clinical care, including surgical and therapeutic options. *Id.* at 18-19.

Patent monopolies on human genes eliminates competition, likely resulting in higher prices, diminished patient access, and decreased quality in genetic testing. See Klein, *supra* at 82. Generally, patients have greater access to genetic tests within competitive markets. Andrew S. Robertson, *The Role of DNA Patents in Genetic Test Innovation and Access,* 9 Nw. J. Tech. & Intell. Prop. 377 at 397-98. Myriad prohibits identifying and allowing researchers to provide numerous, alternative testing methods, including those which are potentially more efficient and cost effective. Robert Cook-Deegan, Subhashini Chandrasekharan & Misha Angrist, *The Dangers of Diagnostic Monopolies,* 458 Nature 405 (2009). Costs per mutation were five times as high using Myriad's test than those developed and used in Europe. *Report* at A-27. Myriad's patents deny a patient access to a confirmatory test from a different laboratory, even when initial tests are inconclusive. *Id.*

Myriad's patents restrict the development of improvements in the quality of genetic tests. Clinical geneticists outside of Myriad's laboratories cannot determine the accuracy of Myriad's test in identifying mutations in the BRCA genes or predicting a patient's risk for breast or ovarian cancer. Using Myriad's test, non-clinical researchers found 10-20% of false negatives in high risk patients. Walsh T., Casadei S., Coat KH et al., *Spectrum of Mutations in BRCA 1, BRCA 2, CHEK and TP 53 in Families at High Risk of Breast Cancer*, 295 JAMA 1379 (2006). Using an alternative molecular testing method one study found that Myriad's test missed up to 12% of large genomic deletions or duplications, *id* at 1380, potentially causing grave harms.

Myriad's patents prevent laboratories from offering more rapid and cost effective methods, such as genomic capture and massive parallel sequencing for multiple breast and ovarian cancer susceptibility genes. King, *supra* at 4. If a result based upon the Myriad test is negative, testing for *other* breast or ovarian cancer genes are done selectively, costing thousands of dollars beyond the costs of Myriad's test. *Id.* With improved technology not used in Myriad's test, mutations can be identified in 21 known breast and ovarian cancer genes in one sample for less than $1500.00, and with further indexing and bar-coding strategies, it can be done for less than $500.00 per sample. *Id.* Myriad's basic test is $3,300.00; its additional analysis test is $700.00.

Myriad's test is also less accurate than new methods, one of which evaluated multiple genes in addition to BRCA 1/2, identifying a wide range of mutations in a variety of genes. *Id.* Six large deletions and duplications were

identified which could have been missed using Myriad's standard test. *Id.* Innovative new comprehensive parallel testing of multiple cancer susceptibility genes cannot be done on the BRCA 1/ 2 sequences without infringing Myriad's patents on isolated DNA.

Socio-economically disadvantaged women and women of ethnic and racial minorities are disproportionately harmed by Myriad's exclusive and broad patents. There is less access to genetic testing for underserved ethnic and racial minorities than for those in the white population. Armstrong K., Micco E., Carney A. et al, *Racial Differences in the Use of BRCA 1/2 Testing Among Women with a Family History of Breast or Ovarian Cancer,* 293 JAMA 1729 (2005). African-American women are 78% less likely to use genetic BRCA testing than white women, and although less diagnosed, they are more likely to die from the disease. *Id.*

The price of Myriad's standard test is necessarily prohibitive. Access to Myriad's test is severely limited for those without insurance, and even for the insured, the coverage for BRCA testing has been inconsistent and reimbursement is limited to those at high risk. *Report* at 37-38. The supplemental BART test is indicated for *all* patients with histories suggesting BRCA 1/2 mutations, however if a patient does not meet Myriad's defined criteria, the test is an additional $700.00. K.M. Shannon et al., *Which Individuals Undergoing BRCA Analysis Need BART Testing?* 204 Cancer Genetics 416 (2011). While some insurers reimburse the additional costs, others consider BART to be an investigational test, excluded from coverage. *Id.*

Myriad's patents also affect the quality of the tests for ethnic and racial minority women. Large genomic deletions or duplications, known as large genetic rearrangements will be found in approximately 12% of patients with both breast cancer and a "severe" family history who test negative for the BRCA genes. *Id.* Data from Myriad suggests that these large rearrangements BRCA mutations are over-represented and account for a larger percentage of mutations than previously thought in some populations, e.g., 20% of Latina women. *An Open Letter to Myriad Genetics,* Friday, July 22, 2011, *available at* http://yalecancergeneticcounseling.blogspot.com/2011_07_11 archive. html.

Lack of access to Myriad's tests for underserved racial and ethnic populations diminishes the quality of the test itself. Michael J. Hall, Olufunmilay I. Olopade, *Disparities in Genetic Testing: Thinking Outside the BRCA Box,* 24. J. Clin. Oncol. 2197 (2006). Models to assess risk used in BRCA testing need accurate estimates of the prevalence in specific populations to estimate probabilities in particularly high risk genotypes. *Id.* However the prevalence of Ashkenazi groups in testing shows a 10 fold increased prevalence in this group compared with estimates for the remaining U.S. population. *Id.* Without accurate estimates of mutation prevalence in minority subgroups, the reliability of these models is compromised. *Id.*

The preemption of the laws of nature, the embodied information of the BRCA 1/2 genes inhibits progress in biomedical research and treatment with serious and harmful implications for the health of women, particularly women who are underserved and socio-economically

disadvantaged, as well as women of ethnic and racial minorities.

CONCLUSION

For the foregoing reasons, the petition for writ of certiorari should be granted.

Respectfully submitted,

Debra Greenfield
Counsel of Record
Institute for Society and Genetics
University of California,
Los Angeles
1323 Rolfe Hall
Box 957221
Los Angeles, CA 90095
(310) 267-4990
dgreenf@ucla.edu

Attorney for Amici Curiae